

Risk factors of severe tuberculosis in children in Surabaya Indonesia

Shirley Ferlina Lasmono¹, Retno Asih Setyoningrum¹, Satrio Boediman¹, Dominicus Husada^{1*}

¹Department of Child Health, Faculty of Medicine
Universitas Airlangga / Dr. Soetomo Hospital, Surabaya, Indonesia

*Corresponding author

Background: Indonesia is a country with the second highest number of tuberculosis (TB) patients. Until today the efforts to tackle the TB problem cannot reduce the incidence significantly. Severe tuberculosis is a fatal form with severe clinical symptoms and complication, mainly miliary and meningitis TB. Identifying the risk factors of severe TB will enable the clinician to do the early detection and treatment.

Objective: To explore the risk factors for severe tuberculosis in children.

Methods: A medical record based, case control study, involving tuberculosis children below the age of 14 was done in Dr. Soetomo Hospital. The hospital is the second largest in the country. It has 2000 beds, including 200 for babies and children. The outpatient clinics were visited by at least 5000 people all ages every working day. The pediatric TB patients were managed at the pediatric respirology outpatient clinic, which was opened twice per week. At least 50 patients would come on each active day. We looked at the data from 2010-2017 of the pediatric outpatient clinic. The cases were defined as children who were diagnosed with miliary and or meningoencephalitis tuberculosis. The controls were TB patients other than miliary TB and or meningoencephalitis TB. The samples were collected randomly with a ratio of 1:1. We collected the data at the time of first visit, including the age, nutritional state, tuberculosis contact and BCG immunization state. Diagnosis of tuberculosis was based on Indonesian Clinical Guidelines for Pediatric Tuberculosis which include clinical condition, pediatric TB scoring system, TB skin test, sputum analysis, and genexpert. Severe TB means miliary TB and or meningoencephalitis TB. Diagnosis of TB Tuberculosis contact was defined as close contact for more than two weeks with TB patient. Age was divided into more than and below two years old, while nutritional state was divided into normal and undernutrition. We used Chi square and logistic regression tests with 95% CI and $p < 0.05$ considered as significant.

Results: From 506 children with TB registered at pediatric respirology outpatient clinic, 124 children were evaluated, comprised of 62 cases and 62 controls. Patients with incomplete medical record data were not included. Only 31.5% were under two years of age, meanwhile, 87.9% received BCG vaccine. The identified risk factors were tuberculosis contact (OR 7.9; 95% CI =3.3-18.7; $p < 0.001$) and nutritional state (OR 2.9; 95% CI =1.1-7.6; $p = 0.033$). The age and the BCG immunization state were not significantly related to severe tuberculosis.

Conclusion: History of contact and nutritional state are the risk factors associated with severe tuberculosis in children in Surabaya, Indonesia.

Keywords: severe tuberculosis, miliary TB, meningoencephalitis TB, children, risk factors

Study subjects

These were children, aged 2 months – 14 years diagnosed with tuberculosis. The child was registered as patient in pediatricrespirology outpatient clinic.

Study setting

The site of this study was Pediatric Respiriology outpatient clinic, dr. Soetomo Hospital, which is located in the Surabaya, East Java. The clinic serves as referral center from east region of Indonesia.

Source of Data

Patient data were obtained from paper-based medical records of respirology outpatient clinic. The data obtained was baseline data at the time of patient enrollment, included the following variables: sex, age, nutritional state, history of tuberculosis contact, BCG immunization state, and diagnosis.

Study Procedure

Children aged 2 months – 14 years diagnosed with tuberculosis who has complete medical record were involved. Diagnosis of tuberculosis was based on Indonesian Clinical Guidelines for pediatric tuberculosis which include clinical, pediatric tuberculosis scoring system, tuberculin skin test result, sputum analysis, and genexpert. Medical records included in this study were divided in to two groups, severe and non-severe tuberculosis.

Operational definitions

In this study, a child diagnosed as meningitis and or milliary tuberculosis was considered as a case of severe tuberculosis, while other forms were considered as control group. The age group was divided in to under and above two years old.

Nutritional state adjusted for sex and age were determined from subjects' weight and height using the WHO curve for children under five years of age and CDC curve for children above 5 years of age. A WHO weight-for-length Z score (WLZ) of < -2 or ideal body weight percentage $< 80\%$ was considered as undernutrition.

Tuberculosis contact was defined as history of close contact with bacteriologically confirmed (smear positive) tuberculosis patients for 2 weeks or more. State of BCG immunization was determined from BCG scar in the right arm and patients' immunization record.

Statistical analysis

The association between each independent variables and severe tuberculosis was examined using the chi square or Fisher's exact test. Univariate and bivariate logistic

regression models were fitted to determine the risk factors for development of severe tuberculosis. Results were expressed as odds ratios (Ors) with their 95% confidence intervals (CIs). Analyses were performed using SPSS software version 25 for Mac and all tests were two sided, with a p-value of <0.05 considered statistically significant.

Ethical approval

The study was approved by the Ethics committee of the dr. Soetomo Hospital, Surabaya, Indonesia.

Results

Out of 506 tuberculosis patients admitted at the study time period, 62 of them were diagnosed as severe tuberculosis, giving an overall severe tuberculosis prevalence of 12.3% in which % suffered from miliary tuberculosis and % suffered from meningoencephalitis tuberculosis. Then, 62 patients with non severe tuberculosis were randomly chosen as controls. The total number of subjects in this study was 124.

In the entire 124 children, the majority were (%) males, ≥ 2 years of age (68.5%), and undernutrition (66.9%). Most of them had already performed BCG immunization (87.9%), and had been exposed to tuberculosis contacts (54.8%) (Table 1).

Table 1. Characteristics of subjects

Patient characteristics	N = 124	(%)
Sex		
Male		()
Female		()
Age		
< 2 years old	39	(31.5)
≥ 2 years old	85	(68.5)
Nutritional state		
Undernutrition	41	(33.1)
Normal	83	(66.9)
BCG immunization Status		
Yes	109	(87.9)
No	15	(12.1)
Tuberculosis contacts		
Yes	68	(54.8)
No	56	(45.2)

On bivariate analysis of the possible risk factors showed that nutritional state and history of tuberculosis contact were significantly associated with severe tuberculosis in children (Table 2). Multivariate logistic regression analyses showed that the risk of having tuberculosis were higher in patients who had tuberculosis contact ($p < 0.01$) and undernutrition ($p = 0.03$) (Table 3).

Table 2. Bivariate analysis of severe tuberculosis risk factors in children

Variables	Cases N (%)	Controls N (%)	OR	95% CI	p-value
Age					
<2 years	20 (47.6)	19 (30.6)	0.9	0.435 – 1.981	1.00
≥ 2 years	42 (52.4)	43 (69.4)			
Nutritional status					
Undernutrition	31 (50)	10 (16.1)	2.9	1.1 – 7.6	0.03
Normal	31 (50)	52 (83.9)			
BCG immunization status					
No	10 (16.1)	5 (8.1)	2.2	0.703 – 6.837	0.27
Yes	52 (83.9)	57 (91.9)			
Tuberculosis contacts					
Yes	50 (80.6)	18 (29)	7.9	3.3 – 18.7	<0.01
No	12 (19.4)	44 (71)			

Table 3. Multivariate model of severe tuberculosis risk factors in children

Variables	Exp (B)	95% CI	p value
Age	0.999	0.398 – 2.511	0.998
Nutritional status	2.878	1.087 – 7.621	0.033
BCG immunization status	1.378	0.335 – 5.669	0.657
Tuberculosis contact	7.848	3.288 – 18.731	<0.01
HIV infection	1,356	0,291 – 6,328	0,698

Table 4. Multivariate analysis of severe tuberculosis risk factors in children

Variables	Exp (B)	95% CI	p value
Nutritional status	27,814	5,570 – 138,880	<0.001
Tuberculosis contact	155,632	28,847 – 839,656	<0.001
<i>Constant</i>	0,087		<0,001

Discussion

Our findings support the previous studies that tuberculosis infection develops as a result of factors such as tuberculosis contact and nutritional status. Nutrition plays an essential role to develop the appropriate innate and Th1 immune responses against tuberculosis [8]. The relationship between nutritional status and the incidence of severe tuberculosis is owing to Th1 cells, which act as an important component in the

cell-mediated immune system defense against *Mycobacterium tuberculosis* (MTB). (Jaganath, 2012) Cell-mediated immune system is a key factor in host defense mechanism against the progression of tuberculosis infection to active TB disease (cegilski, J.P. 2004). Therefore, Th-1 immunity against tuberculosis is impaired by malnutrition, so increases the risk of developing severe tuberculosis. Study in guinea pigs given a low protein diet and then exposed to *M. tuberculosis* have deficits in mounting an appropriate Th1- type cell-mediated response. This includes decreased lymphocyte proliferation, higher immunoglobulin G levels, and decreased cytokines such as IL-2, TNF- α , and IFN- γ [28], so these animals have evidence of worse disease, with higher bacillary load in the lung and spleen (29). Nutrition has a profound effect on the Th-1 immune system's ability to defend against tuberculosis soon after infection and thus predisposes the animal to disease progression. (Jaganath, 2012) Recent study from Lienhardt discovered that severe malnutrition was shown to depress immune responsiveness to BCG, although there was some uncertainty about the effect of mild malnutrition. (Lienhardt, C. 2003)

Children who are in close contact with individuals with tuberculosis are at high risk of developing TB. Despite the former vaccination with BCG, it has been suggested that a positive TST in a child who has close contact with an adult with infectious TB most likely represents infection with *M. tuberculosis*. Sloot et al (2014) reported the risk of coprevalent and incident TB among contacts with LTBI aged less than 5 years was about twice the risk among contacts aged 5–14 years, and the risk among contacts aged 5–14 years was almost three times the risk among contacts aged greater than or equal to 15 years.

BCG immunization status coverage in this study was high. The estimated efficacy of BCG prevention from miliary TB reached 77%, but in Asian countries that already have high immunization coverage, the efficacy estimation could be decreased (Trunz B. 2006). BCG has 60-80% protective efficacy against severe forms of tuberculosis in children, particularly meningitis (rodrigus, L. C. 2011; Trunz, B. B. 2006), and its efficacy against pulmonary diseases varies geographically, depending on the method of administration, vaccine strain used and nutritional status at time of vaccination (Menzies, R. 1992; Colditz, G. A. 1994; Zodpey, S. P. 2007). BCG does not seem to protect against disease when it is given to people already infected or sensitized to environmental mycobacteria, which could explain the geographical variation (Abubakar I, 2012; Narayanan, P. R. 2006; Mangtani, P. O. 2013). Indonesia's

latitude and longitude is 5° 00'N and 120° 00' E. Study from Mangtani, et al (2013) concluded that there was no evidence of protection against infection less than 40° latitude away from the equator. A recent meta-analysis of trials, including 18 studies reporting on protection against pulmonary and six reporting on protection against miliary or meningeal tuberculosis, showed no evidence that efficacy of BCG was associated with vaccination strains (Mangtani, P. 2012). Future trials of candidate vaccines need to investigate the efficacy of the new vaccine against tuberculosis infection and early progression and late progression to active disease.

Age of the patient had not significant association with developing of severe tuberculosis. This finding may be affected by the higher prevalence of elder pediatric tuberculosis patients in this study. Marais et al (2004) alluded that eventhough age under two years old was at risk of military TB, but most children suffering from tuberculosis in endemic areas were elder that two years, so there is a higher chance of children over two years of age suffer from military tuberculosis. Kruijshaar and Abubakar from their study in UK discovered that more incidences of military tuberculosis occurred in elder age children, which indicated the possibility of reactivation of latent disease. Thus results support that severe forms tuberculosis are able to happen in any ages.

Conclusion

This study showed that nutritional state and history of tuberculosis contact associate with incidence severe tuberculosis.

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Dominicus Husada
Pediatrics
School of Medicine of Airlangga University / Dr. Soetomo Hospital
Kertajaya Indah VII / 9 (G-121)
Surabaya, East Java 60116
Indonesia

A3: Tuberculosis: Mechanisms, Pathogenesis and Treatment

Dear Dominicus Husada,

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The conference will be held during the dates of January 17— 21, 2019, at the Fairmont Banff Springs, Banff, Alberta, Canada. We know you will find the networking opportunities as well as the dynamic research presented a value to your scientific future.

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Keystone Symposia and the scientific organizers Christina L. Stallings, Veronique Anne Dartois, Stewart T. Cole and David Barros thank you for your participation in this meeting.

Sincerely,



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